Journal of the Formosan Medical Association (2015) 114, 722–728

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

Cost-effectiveness analysis of carrier and prenatal genetic testing for X-linked hemophilia

Meng-Che Tsai [a], Chao-Neng Cheng [a], Ru-Jay Wang [b], Kow-Tong Chen [b], Mei-Chin Kuo [c], Shio-Jean Lin [a,c,*]

[a] *Department of Pediatrics, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[b] *Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[c] *Department of Pediatrics, Chi-Mei Hospital, Tainan, Taiwan*

Received 31 January 2013; received in revised form 13 May 2013; accepted 19 June 2013

KEYWORDS
carrier testing;
economic analysis;
ethics;
hemophilia;
prenatal diagnosis

Background/purpose: Hemophilia involves a lifelong burden from the perspective of the patient and the entire healthcare system. Advances in genetic testing provide valuable information to hemophilia-affected families for family planning. The aim of this study was to analyze the cost-effectiveness of carrier and prenatal genetic testing in the health-economic framework in Taiwan.
Methods: A questionnaire was developed to assess the attitudes towards genetic testing for hemophilia. We modeled clinical outcomes of the proposed testing scheme by using the decision tree method. Incremental cost-effectiveness analysis was conducted, based on data from the National Health Insurance (NHI) database and a questionnaire survey.
Results: From the NHI database, 1111 hemophilic patients were identified and required an average medical expenditure of approximately New Taiwan (NT) $2.1 million per patient-year in 2009. By using the decision tree model, we estimated that 26 potential carriers need to be tested to prevent one case of hemophilia. At a screening rate of 79%, carrier and prenatal genetic testing would cost NT $85.9 million, which would be offset by an incremental saving of NT $203 million per year by preventing 96 cases of hemophilia. Assuming that the life expectancy for hemophilic patients is 70 years, genetic testing could further save NT $14.2 billion. Higher screening rates would increase the savings for healthcare resources.
Conclusion: Carrier and prenatal genetic testing for hemophilia is a cost-effective investment in healthcare allocation. A case management system should be integrated in the current

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

* Corresponding author. Department of Pediatrics, Chi-Mei Hospital, 901 Jhonghua Road, Yongkang District, 710 Tainan, Taiwan.
E-mail address: shiojean@gmail.com (S.-J. Lin).

http://dx.doi.org/10.1016/j.jfma.2013.06.017

practice to facilitate patient care (e.g., collecting family pedigrees and providing genetic counseling).

Introduction

Hemophilia A and hemophilia B are X-linked recessive bleeding disorders caused by a deficiency of factor VIII and factor IX, respectively. Males with defective genes are symptomatic with diverse clinical severity, whereas females are usually asymptomatic carriers of the genes. The worldwide occurrence is estimated to affect 1 per 5000 newborn males for hemophilia A and 1 per 30,000 newborn males for hemophilia B.[1] Patients and their families may bear a heavy disease burden associated with uncertain and excessive bleeding, risks of transfusion-related infection, frequent outpatient and inpatient visits, loss of life quality, and care-related emotional distress.[2–5] Because the development of recombinant clotting factors has greatly improved the healthcare and health status of hemophilic patients, financial expenditures on hemophilia-related treatments are expanding, largely because of the growing costs of these novel pharmacological therapies.[6,7] To effectively reduce the recurrence of this disease, it is important to provide as much medical information as possible for the decision-making of families at risk for hemophilia.[8]

Attitudes towards genetic testing in the hemophilia community also need to be considered. Many individual and socioenvironmental factors may influence the option of predictive and carrier testing for inherited diseases.[9] Discussions usually involve who can give consent and when to perform the test.[10–12] The main concerns include disclosure of genetic confidentiality, psychosocial stigmatization, emotional distress of future disabilities, and prenatal violation of the right to life if artificial abortion is adopted.[13–15] However, both healthcare providers and the hemophilia community also argue the potential advantages of genetic testing in that it may provide anticipatory guidance in healthcare for affected patients and fetuses at risk of hemophilia, and it may provide reproductive options for female carriers.[12,16] Therefore, thorough psychosocial evaluation and family counseling may be needed before the implementation of genetic testing in clinical practice.

Screening for hemophilia could previously be performed by testing the level of factor VIII or factor IX coagulation activity in blood.[17,18] Measurement of coagulation activity is correlated with clinical severity; however, this technique is unable to provide genetic information in prenatal diagnosis. Recent advancements in molecular technology have introduced several rapid and sensitive mutational analyses of defective genes.[18–21] Genetic testing of the factor VIII (*F8*) gene and the factor XI (*F9*) gene in carrier screening and prenatal diagnosis for hemophilia is possible and reliable. Costs for this technique are also steadily declining because of technical improvements and massive application. However, overuse of unnecessary genetic testing that is mismatched to health needs may lead to accruement of medical expenditures that exceed the potential savings from disease prevention.[13,22] In a resource-limited setting, a key criterion for funding decisions relies on a certain balance between the economic costs and health benefits. Invasive prenatal sampling of fetal cells incurs a certain risk of miscarriage. Before health authorities provide medical allowances for genetic testing, an economic analysis framework in the context of ethical, social, and legal aspects must be applied.[23] The aim of this study was to investigate the cost-effectiveness of carrier detection and prenatal diagnosis for hemophilia. Results of the economic evaluations are expected to provide insight into the improvement of healthcare for hemophilic patients and their relatives.

Methods

Decision analysis

A decision tree model was applied to evaluate the cost-effectiveness of hemophilia carrier detection and prenatal diagnosis by using the TreeAge Pro decision analysis software (TreeAge Pro 2012; TreeAge Software Inc., One Bank Street Williamstown, MA 01267, USA). We performed economic and clinical comparisons between two hypothesized scenarios—namely, with genetic testing and without genetic testing.

Study participants

To obtain opinions and construct the questionnaire, we performed in-depth interviews with focus groups. Focus group members consisted of hematologists, genetic counselors, sociologists, legal scholars, and hemophilic patients and their family members. For the survey of public opinions regarding genetic testing for hemophilia, healthy females of childbearing age were recruited from multiple sources. Hemophilic patients and their family members were recruited from a convenient sample in two medical centers. All interviews and questionnaire surveys were approved by the Institutional Review Board of the participating hospitals.

Estimates of attitudes toward prenatal screening

A questionnaire was specifically designed to explore attitudes toward prenatal genetic testing. We asked respondents concerning their willingness to receive a carrier and prenatal genetic test for hemophilia, willingness to conceive a baby, and willingness to continue a pregnancy if the prenatal genetic test was positive for hemophilia. To encompass the minimum and maximum prevention effects of the genetic test, we modeled high and low screening rates in our analysis.

Estimates of healthcare costs for hemophilic patients

Economic evaluations of the cost-effectiveness analysis involved medical and nonmedical perspectives. Medical costs included direct expenditures of outpatient and inpatient service use and out-of-pocket healthcare-related expenses (e.g., alcohol swabs and cotton wools), whereas nonmedical costs included loss of work productivity and travel expenses to medical facilities. With regard to comprehensive coverage, direct medical expenditure and the present number of hemophilic patients were retrieved from the database of the National Health Insurance (NHI) program in Taiwan.[24] Annual medical expenditure per person was hence estimated by the annual total medical expenditure divided by the maximum number of hemophilic patients in a single year. We also used the claims data for hemophilia-related healthcare use from the NHI database to obtain an annual estimate of clinical visits per person. Estimation of out-of-pocket healthcare-related expenses and nonmedical costs were based on the results of the aforementioned purposive questionnaire survey conducted on hemophilic patients.

Estimates of costs and accuracy of genetic testing

Methodological differences may affect the accuracy and cost of genetic tests for hemophilia. The combined use of direct sequencing and denaturing high-performance liquid chromatography (DHPLC) could elevate the accuracy rate to 96% and was therefore implemented in our model for analysis.[19,25,26] In current practice, the cost of genetic testing for hemophilia ranges from New Taiwan (NT) $4500 to NT $25,000, depending on the complexity of responsible genes and technical requirements for the analysis of rare or hot mutational spots. Hence, we assumed the highest possible cost of genetic testing in our scenario. The procedure-related cost (e.g., service fees, device expenses, and costs for prenatal amniocentesis and karyotyping) was moreover added into the total cost of the genetic test. We modeled a genetic test costing NT $25,510 and a prenatal chromosome study with amniocentesis costing NT$ 34,000.

Estimates of target population for genetic tests

Because there is no available data regarding the exact number of hemophilic carriers in Taiwan, we assumed 277 potential carrier women for every 100 affected men and that one-half of these potential carriers would be true carriers, based on published literature.[27] We modeled a target population based on the estimated number of present hemophilic patients multiplied by the ratio of potential carrier females to affected males.

Incremental cost-effectiveness analysis

Our prediction model required a number of assumptions. First, we estimated that the life expectancy for hemophilic patients is 70 years. This assumption was based on previous studies showing that hemophilic patients had a shorter life expectancy than the general population by 5–15 years on average.[28,29] Second, we assumed that opportunities for healthcare utilization would be equal throughout the entire lifetime. Third, we assumed that costs and health outcomes in future years would not be discounted or inflated. The incremental costs and savings per hemophilia case that were prevented were calculated by comparing the costs and effects in the hypothesized scenarios with and without genetic tests for hemophilia.

Results

Attitudes toward prenatal screening

Convenience sampling was employed and consisted of 30 hemophilic patients and 41 female relatives of these patients. For their counterparts, 788 healthy females of childbearing age were recruited. Among the female relatives of the hemophilic patients, 79% of the women were willing to receive a genetic test for hemophilia; 71% of the women were willing to have a child if they tested positive as a hemophilia carrier; 85% of the women were willing to have a prenatal screening test if they were pregnant; and 28% of the women with a positive prenatal test for hemophilia were willing to give birth to an affected boy. By contrast, 97% of the healthy females were willing to receive a genetic test for hemophilia if they had hemophilic relatives; 51% of healthy females were willing to have a child if they tested positive as a hemophilia carrier; 98% of healthy females were willing to have a prenatal screening test for hemophilia if they were pregnant; and 33% of healthy females with a positive prenatal test for hemophilia were willing to give birth to an affected boy. Based on the aforementioned results, we modeled high (97%) and low (79%) screening rates in the subsequent cost-effectiveness analysis.

Healthcare costs for hemophilic patients

We employed the claims data for hemophilia-related healthcare from the NHI database. The mean clinical visit value was approximately 25 times for one patient per year. On average, they spent 4 hours (travel time included) for each clinical visit. The minimum wage of NT $98/hour in 2011 was used to calculate the preceding earnings because of clinical visits,[30] and an average amount of NT $220 for travel to and from the medical service was reported by the surveyed patients.

Effects of carrier prenatal genetic tests

From the NHI database, we identified 1111 hemophilic patients in 2009. By multiplying by the ratio of female carriers to male patients, we estimated there were 3078 potential hemophilia carriers in Taiwan. Without any intervention, 196 newborn males are assumed to be affected with hemophilia. According to our scheme for carrier prenatal screening, there would be 2432 potential carriers tested and the prevented births of 96 hemophilic newborns, based on a screening rate of 79%; 554 more carriers would be

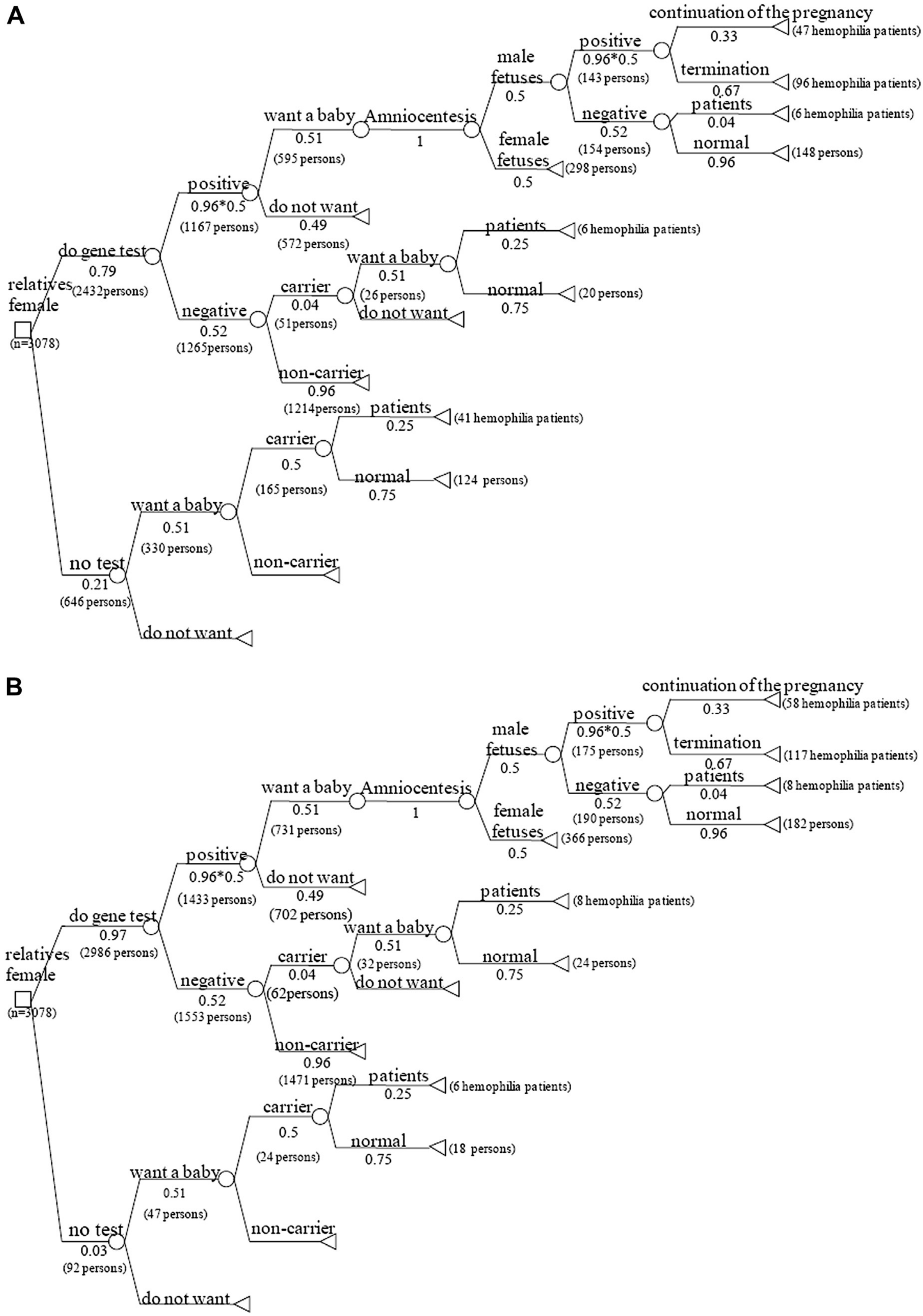

Figure 1 The decision tree model for carrier and prenatal genetic testing for hemophilia at the screening rate of (A) 79% and (B) 97%.

Table 1 Expenditures of medical care for hemophilic patients [in New Taiwan (NT) dollars].

Year	No. of patients	Outpatient costs	Inpatient costs	Total costs	Costs per patient-year	Medication costs	Medication costs (%)
2002	881	784,471,365	73,761,813	858,233,178	974,158	837,517,191	97.59
2003	907	925,273,485	87,742,743	1,013,016,228	1,116,887	994,358,679	98.16
2004	946	1,044,484,666	97,517,372	1,142,002,038	1,207,190	1,119,411,753	98.02
2005	931	1,288,663,531	156,216,322	1,444,879,853	1,551,965	1,420,505,522	98.31
2006	979	1,512,737,373	148,924,092	1,661,661,465	1,697,305	1,635,971,217	98.45
2007	1024	1,770,764,448	175,864,512	1,946,628,960	1,901,005	1,918,712,788	98.57
2008	1068	2,042,505,236	213,003,569	2,255,508,805	2,111,900	2,227,555,725	98.76
2009	1111	2,132,631,605	193,316,456	2,325,948,061	2,093,563	2,296,683,277	98.74

tested and the births of 21 more hemophilic patients would be prevented if the screening rate were augmented to 97% (Fig. 1). The testing of 26 carriers on average is needed to prevent the birth of one hemophilic male newborn.

Healthcare expenditures for hemophilic patients

According to the NHI research database, the registered number of hemophilic patients increased from 881 patients in 2002 to 1111 patients in 2009 (Table 1). The mean number of newly diagnosed patients was 33 patients per year. The direct medical cost for hemophilic patients peaked in 2009 with a total amount of approximately NT $2.1 million per person, but most (98%) of this cost was attributed to pharmacological products. From the patient's perspective, out-of-pocket healthcare-related expenditures cost NT $466 per month, whereas an absence from work costs NT $392 per clinical visit. In total, the healthcare expenditure for hemophilic patients was estimated as NT $2,114,455 per patient-year.

Incremental cost-effectiveness ratio

Table 2 shows the incremental cost-effective ratio of the proposed scheme of carrier and prenatal genetic testing in comparison to the current practice. In the analysis, the total amount of NT $1,219,473 at the screening rate of 79% and NT $1,212,822 at the screening rate of 97% would be saved per life year prevented. Given an average life expectancy of 70 years for hemophilic patients, the sum of savings was estimated to reach NT $8.2 billion at the screening rate of 79% and NT $9.9 billion at the screening rate of 97%.

Discussion

According to the NHI research database, the medical expenditure for hemophilic patients per year has tripled and the medical expenditure per patient-year doubled from the years of 2002 to 2009. The causes of the incremental costs could largely be attributed to growing acquisition prices of novel pharmacological products, evolutional concepts in prophylaxis treatment, advancements in healthcare that result in a longer life expectancy, and increased surgical needs such as arthroplasty.[7,23,31] Many previous studies comparing the cost-effectiveness between prophylactic use and on-demand use of coagulation factors have been in favor of adding the costs of prophylaxis treatment that prevent bleeding episodes.[28,32] The demand for therapeutic treatment nevertheless remains an expanding burden on healthcare resources.[33,34] The number of newly diagnosed patients therefore has not reduced. We observed that recurrent hemophilic patients from the same carrier mother were rare, but prenatal screening was not prevalent

Table 2 Estimates of health outcomes with and without genetic testing.

Events, *n*	No genetic testing	79% Screening rate	97% Screening rate
Hemophilic patients	196	100	79
Terminated hemophilic fetuses	0	96	117
Costs for hemophilia care, NT $			
Direct medical costs	410,338,348	209,356,300	165,391,477
Healthcare-related costs	1,096,032	559,200	441,768
Non-medical costs	2,998,800	1,530,000	1,208,700
Total costs	414,433,180	211,445,500	167,041,945
Costs for genetic testing, NT $			
Costs for carrier genetic testing	0	62,040,320	76,172,860
Costs for amniocentesis and chromosome study	0	20,230,000	24,854,000
Costs for fetal genetic testing	0	3,647,930	4,464,250
Total costs	0	85,918,250	105,491,110
Incremental cost-effectiveness ratio		1,219,473	1,212,822

NT $ = New Taiwan dollars.

among female relatives of affected males. There were also sporadic cases, comprising 30% of the hemophilia community, that are unpreventable by carrier testing.[1,31] With the advancement of molecular technology, accurate prenatal diagnosis has been proven to be achievable and effective in preventing the birth of children with hemophilia.[35]

Based on the decision tree method, our analysis suggests that investment in genetic testing for potential carriers in hemophilic families will yield cost savings in healthcare expenditures related to this disease. Having 26 potential pregnant carriers receive prenatal screening would add an approximate incremental cost of NT $1.6 million, but prevent the birth of a newborn with hemophilia, which is a saving of NT $2.1 million per life year and will avert a total of 70 life years per patient. To maximize the effect size of our proposed diagnostic scheme, the screening rate is an important determinant of its success. At an additional cost of NT $19.6 million to increase the screening rate from 79% to 97%, we expect to prevent 21 more cases of hemophilia, and consequently further save 1470 life years and NT $3 billion in future costs. A case management system has been introduced as a practical and integrative tool in the field of healthcare for hemophilic patients. Such a healthcare system may facilitate collecting family pedigrees, identifying potential female carriers, coordinating health professionals in providing health services, counseling patients and families about diseases, and hence may increase the likelihood of accepting genetic testing.[34,36]

Another factor that warrants attention is the ethical issues raised in the discussion of providing genetic testing to the hemophilia community. Universal screening may violate personal genetic privacy and deprive patients of the right to consent in medical care.[12,13,15,22] Decisions regarding receiving prenatal diagnosis and termination of affected pregnancies are complex and determined by personal, cultural, and ethical factors.[9,11,37] Prenatal diagnosis should not simply be used as a justification for reproductive termination. In our survey, a lower percentage of hemophilic families opted for genetic testing compared to their healthy counterparts. Possible reasons hemophilic families less frequently opt for genetic testing include the fear of conceiving an affected baby, guilty feelings and/or denial of being the carrier of the causative genes, and abstention from reproduction. Some people were also concerned about revealing the genetic results to their partner because this would cause pressure on the carriers because of the stigmatization of this disease. By contrast, options for genetic testing were primarily for the sake of medical care and lifestyle. For example, if a female relative of a hemophiliac knows she is a carrier, she may wish to know how to prevent the occurrence in future pregnancies or prepare for specific obstetrical precautions. Because of this, genetic counseling is vital before and after diagnostic testing for hemophilia. Female relatives at risk of having a carrier status should be advised of the possible psychological impacts resulting from the outcome of predictive testing. The decision of to whom to disclose the hereditary information also needs to be individualized in the counseling discussion.

There are some limitations in the present study in interpreting the results. First, our estimation was primarily based on the NHI database. We were unable to access individual insurance claims and therefore assumed that medical expenditure was equal across all ages. However, demands for hemostatic therapy are mostly dependent on the level of physical activity and risk of trauma, which peak in young adulthood.[28] Costs for hemophilia treatment per life year may be overestimated in the first several years of childhood. In actuality, children with hemophilia require lifelong therapy that eventually equals the costs of prenatal testing. Second, the diagnostic process is modified for simplicity in our scenario-based analysis. The index case may need genotyping in the very beginning before the female relatives receive carrier testing. A sequential genotyping strategy is required for detecting a vast variety of genetic defects such as inversion, insertions or deletions, and point mutations. These techniques may include polymerase chain reaction for detecting intron inversions, DHPLC, or newer techniques such as high-resolution melting analysis (for detecting small insertions and deletions) and direct sequencing (for detecting point mutations).[19,26,38] Despite the evolution of molecular techniques, the feasibility of genetic testing in hemophilia A and hemophilia B should warrant cautious attention that mutant alleles may exist beyond the scope of our current examination. The cost-effectiveness of our proposed scheme can be influenced by the proportion of pregnancies in which the women opt for termination. Reproductive opinions expressed by the limited number of hemophilic families in this study may not be generalized to the whole community. Further research on the attitudes toward and beliefs about genetic testing among Taiwanese patients and their families is needed to tailor the policy so that it is more applicable to local situations.

In conclusion, carrier and prenatal genetic testing for hemophilia is a cost-effective investment in saving future healthcare expenditures of this disease. We recommend that prenatal genetic diagnosis should be promoted under ethical, social, and legal aspects. In current practice, a case management system should meanwhile be integrated for its benefits in improving the efficiency of healthcare provided to patients and families.

Acknowledgments

This study was funded by the Bureau of Health Promotion, Department of Health, Taiwan (DOH99-HP-1210).

Reference

1. Mannucci PM, Tuddenham EG. The hemophilias—from royal genes to gene therapy. *N Engl J Med* 2001;**344**:1773—9.
2. Neufeld EJ, Recht M, Sabio H, Saxena K, Solem CT, Pickard AS, et al. Effect of acute bleeding on daily quality of life assessments in patients with congenital hemophilia with inhibitors and their families: observations from the dosing observational study in hemophilia. *Value Health* 2012;**15**:916—25.
3. Trimble SR, Parker CS, Grant AM, Soucie JM, Reyes N. Assessing emerging infectious threats to blood safety for the blood disorders community. *Am J Prev Med* 2010;**38**(Suppl. 4):S468—74.
4. Bullinger M, Von Mackensen S. Quality of life in children and families with bleeding disorders. *J Pediatr Hematol Oncol* 2003;**25**(Suppl. 1):S64—7.

5. Coppola A, Cerbone AM, Mancuso G, Mansueto MF, Mazzini C, Zanon E. Confronting the psychological burden of haemophilia. *Haemophilia* 2011;**17**:21—7.
6. Berntorp E, Shapiro AD. Modern haemophilia care. *Lancet* 2012;**379**:1447—56.
7. Valentino LA, Pipe SW, Tarantino MD, Ye X, Xiong Y, Luo MP. Healthcare resource utilization among haemophilia A patients in the United States. *Haemophilia* 2012;**18**:332—8.
8. Carcao MD. The diagnosis and management of congenital hemophilia. *Semin Thromb Hemost* 2012;**38**:727—34.
9. Balak DM, Gouw SC, Plug I, Mauser-Bunschoten EP, Vriends AH, Van Diemen-Homan JE, et al. Prenatal diagnosis for haemophilia: a nationwide survey among female carriers in the Netherlands. *Haemophilia* 2012;**18**:584—92.
10. Sorenson JR, Jennings-Grant T, Newman J. Communication about carrier testing within hemophilia A families. *Am J Med Genet C Semin Med Genet* 2003;**119C**:3—10.
11. Thomas S, Herbert D, Street A, Barnes C, Boal J, Komesaroff P. Attitudes towards and beliefs about genetic testing in the haemophilia community: a qualitative study. *Haemophilia* 2007;**13**: 633—41.
12. Borry P, Fryns JP, Schotsmans P, Dierickx K. Attitudes towards carrier testing in minors: a systematic review. *Genet Coun* 2005;**16**:341—52.
13. Rogowski WH, Grosse SD, John J, Kaariainen H, Kent A, Kristofferson U, et al. Points to consider in assessing and appraising predictive genetic tests. *J Community Genet* 2010; **1**:185—94.
14. Wang MR, Lin SJ, Tsai WH. Qualitative analysis of the ethical implications of genetic counseling for medical staff of the pediatric and obstetrics. *Tzu Chi Med J* 2004;**16**:111—8 [in Chinese, English abstract].
15. Wilcken B. Ethical issues in genetics. *J Paediatr Child Health* 2011;**47**:668—71.
16. Dunn NF, Miller R, Griffioen A, Lee CA. Carrier testing in haemophilia A and B: adult carriers' and their partners' experiences and their views on the testing of young females. *Haemophilia* 2008;**14**:584—92.
17. Karimi M, Bereczky Z, Cohan N, Muszbek L. Factor XIII Deficiency. *Semin Thromb Hemost* 2009;**35**:426—38.
18. Gomez K, Chitlur M. Survey of laboratory tests used in the diagnosis and evaluation of haemophilia A. *Thromb Haemost* 2013;**109**:738—43.
19. Lin SY, Su YN, Hung CC, Tsay W, Chiou SS, Chang CT, et al. Mutation spectrum of 122 hemophilia A families from Taiwanese population by LD-PCR, DHPLC, multiplex PCR and evaluating the clinical application of HRM. *BMC Medical Genet* 2008;**9**:53. http://dx.doi.org/10.1186/1471-2350-9-53.
20. Berber E, Leggo J, Brown C, Gallo N, Feilotter H, Lillicrap D. DNA microarray analysis for the detection of mutations in hemophilia A. *J Thromb Haemost* 2006;**4**:1756—62.
21. Chan K, Sasanakul W, Mellars G, Chuansumrit A, Perry D, Lee CA, et al. Detection of known haemophilia B mutations and carrier testing by microarray. *Thromb Haemost* 2005;**94**: 872—8.
22. Grosse SD, Rogowski WH, Ross LF, Cornel MC, Dondorp WJ, Khoury MJ. Population screening for genetic disorders in the 21st century: evidence, economics, and ethics. *Public Health Genomics* 2010;**13**:106—15.
23. Escobar MA. Health economics in haemophilia: a review from the clinician's perspective. *Haemophilia* 2010;**16**(Suppl. 3): S29—34.
24. Chang RE, Lin W, Hsieh CJ, Chiang TL. Healthcare utilization patterns and risk adjustment under Taiwan's National Health Insurance system. *J Formos Med Assoct* 2002;**101**:52—9.
25. Oldenburg J, Ivaskevicius V, Rost S, Fregin A, White K, Holinski-Feder E, et al. Evaluation of DHPLC in the analysis of hemophilia A. *J Biochem Biophys Methods* 2001;**47**:39—51.
26. Chen YC, Hu SH, Cheng SN, Chao TY. Genetic analysis of haemophilia A in Taiwan. *Haemophilia* 2010;**16**:538—44.
27. Kasper CK, Lin JC. How many carriers are there? *Haemophilia* 2010;**16**:842.
28. Liou WS, Tu TC, Cheng SN, Chou TY, Lee CF, Lin TK, et al. Secondary prophylaxis treatment versus on-demand treatment for patients with severe haemophilia A: comparisons of cost and outcomes in Taiwan. *Haemophilia* 2011;**17**:45—54.
29. Triemstra M, Rosendaal FR, Smit C, Van der Ploeg HM, Briet E. Mortality in patients with hemophilia. Changes in a Dutch population from 1986 to 1992 and 1973 to 1986. *Ann Intern Med* 1995;**123**:823—7.
30. Council of Labor Affairs, Taiwan. *Minimum wage in Taiwan*. Available at http://www.cla.gov.tw/cgi-bin/siteMaker/SM_theme?page=4e12daf9; [accessed 15.11.2012].
31. Bolton-Maggs PH, Pasi KJ. Haemophilias A and B. *Lancet* 2003; **361**:1801—9.
32. Colombo GL, Di Matteo S, Mancuso ME, Santagostino E. Cost-utility analysis of prophylaxis versus treatment on demand in severe hemophilia A. *Clinicoecon Outcomes Research* 2011;**3**: 55—61.
33. Guh S, Grosse SD, McAlister S, Kessler CM, Soucie JM. Health care expenditures for Medicaid-covered males with haemophilia in the United States. *Haemophilia* 2008;**2012**(18): 276—83.
34. Johnson KA, Zhou ZY. Costs of care in hemophilia and possible implications of health care reform. *Hematology Am Soc Hematol Educ Program* 2011;**2011**:413—8.
35. Sasanakul W, Chuansumrit A, Ajjimakorn S, et al. Cost-effectiveness in establishing hemophilia carrier detection and prenatal diagnosis services in a developing country with limited health resources. *Southeast Asian J Trop Med Public Health* 2003;**34**:891—8.
36. O'Shea E, Coughlan M, Corrigan H, McKee G. Evaluation of a nurse-led haemophilia counselling service. *Br J Nurs* 2012;**21**: 864—6. 868—870.
37. Kadir RA, Sabin CA, Goldman E, Pollard D, Economides DL, Lee CA. Reproductive choices of women in families with haemophilia. *Haemophilia* 2000;**6**:33—40.
38. Ma GC, Chang SP, Chen M, Kuo SJ, Chang CS, Shen MC. The spectrum of the factor 8 (F8) defects in Taiwanese patients with haemophilia A. *Haemophilia* 2008;**14**:787—95.